their allowance. Applicants accordingly respectfully request favorable reconsideration and allowance.

Acknowledgement by the PTO of the receipt of applicants' papers filed under §119 is noted.

The previously pending claims have been replaced by new claims 54-93, which in most cases are re-presentations of previously pending claims. These claims are patentable for the reasons pointed out below in response to the rejections of record.

Claim 41 has been rejected under the second paragraph of §112. The problem raised by the Examiner no longer exists.

Claims 31-33, 38-40, 42-44, 50, 51 and 53 have been rejected as anticipated by Fondy WO '293. This rejection is respectfully traversed.

Claim 31 has been replaced by new claim 54, the latter of which specifically makes clear that the treatment involves at least two non-consecutive administrations of liposomal cytokine, as indicated in the examples according to which the liposomal cytokine is administered on days 7, 10 and 14. In addition, original claim 21 has been amalgamated with previous claim 38 to specifically define the requirement of a

time interval between the administration of the chemotherapeutic drug and of the first amount of the encapsulated cytokine, the encapsulated cytokine being administered following administration of the chemotherapeutic drug.

A similar amendment was made in previous claim 42 (corresponding to new claim 72), which has been amalgamated with previous claim 53. As a result,, claims 38 and 53 are deleted.

Claims 55 and 73 are newly added and define a time interval between administration of the chemotherapeutic drug and cytokine of at least three days. Support for this requirement may be found in the specification (according to the English language text of the international publication), in page 8, lines 23-24 "*Free adriamycin or DOXIL™, respectively, were administered intravenously on day 7 (8mg/kg), **followed 3 days** later by intravenous cytokine treatment.*" and on page 9, lines 13-14 "*Free adriamycin or DOXIL™ (8mg/kg) were administered intraperitoneally 7 days later by intravenous cytokine treatment*"; as well as in other locations throughout the description.

As will be explained below, the time interval between administration of the chemotherapeutic drug and the cytokine is essential for achieving an effective treatment.

Returning to the rejection under §102, the Examiner's attention is respectfully invited to the last five lines of claim 54 which focuses on the time interval between administrations. Claim 72 differs from claim 54 in that the chemotherapeutic drug is encapsulated in liposomes.

The rejection says that Fondy teaches the use of a liposomal encapsulation of IL-2 with MLV as a possible delivery vehicles, and the administration of IL-2 after that of cytochalasin, which may be in liposomes or not, and specifically refers to page 21, which states the IL-2 may be administered **shortly** after administration of cytochalasin.

However, while Fondy merely states that IL-2 should be administered **shortly** after the cytochalasin **in order to reverse the immunosuppressing activity of the cytochalasin** (see page 20, lines 16-17), it does not teach the effect obtained by administering the immunostimulating cytokine a substantial time after administration of a chemotherapeutic drug, the time interval defined as that the therapeutic effect of the combined administrations is greater than the sum of the therapeutic effects produced by administration of said chemotherapeutic drug alone and by administration of said immunostimulating cytokine alone. In addition, Fondy does not teach the requirement of two or more treatments with liposomal cytokine, and the unique regimen of treatment according to

which the cytokine is administered on non-consecutive days. This treatment regimen is required in order to effectively stimulate the immune response after reducing tumor burden by the chemotherapeutic drug.

The time interval between administrations is essential for achieving an effective reduction of tumor burden and elimination of the tumor. According to the method of the present invention a substantial interval is applied between administration of the chemotherapeutic drug and the immunostimulatory cytokine in order to achieve at first a reduction in tumor burden (by the treatment with the chemotherapeutic drug); and only after reaching a minimal residual disease, the immunostimulatory cytokine is administered in two or more doses in order to achieve the complete elimination of the tumor. **Without significantly reducing the tumor burden** (a process which requires a chemotherapeutic drug to be administered a "sizable" amount of time prior to the cytokine; this is to enable the effect of the chemotherapeutic agent to take place before the cytokine is applied), **the cytokine would not be effective in eliminating the remaining tumor.**

Fondy specifically teaches that the interval between the administration of two agents is a very short period, being, as exemplified, 1 hour (see page 20, line 21).

Evidently, this time period between administrations would not be sufficient to achieve substantial reduction in tumor size and would result in an unsuccessful treatment. In addition, it should be noted that according to Fondy, the purpose of the administering IL-2 shortly after chemotherapy is to reverse the immunosuppression caused by the chemotherapeutic drug, whereas the present invention provides the cytokine several days after chemotherapy in order to mobilize and activate the immune system after a reduction in tumor load has been achieved by the drug, rather than reversing the immunosuppression caused by the drug.

Fondy does not anticipate any of applicants' claims, and the rejection should be withdrawn. Such is respectfully requested.

Claims 31-40 were rejected as obvious under §103 from Fondy in view Anderson USP '698 and Ochoa USP '763. This rejection is respectfully traversed.

The subsidiary references do not make up for the above noted deficiencies of Fondy, and indeed have not been cited for that purpose. Therefore, even if the proposed combination were obvious, it would not reach applicants' claims.

Thus, even assuming *ad arguendo* that Anderson and Ochoa suggest how to produce MLV-encapsulated IL-2, their

combination with Fondy would not suggest the specific method of treatment of the present invention which requires that the encapsulated cytokine be administered a substantial time after the administration of the chemotherapeutic drug, the time interval between administrations being such that the therapeutic effect of the combined administrations is greater than the sum of the therapeutic effects produced by administration of said chemotherapeutic drug alone and by administration of said immunostimmulating cytokine alone. The importance of the time interval between administrations is explained above.

Therefore, even if Anderson and Ochoa describe MLV encapsulated IL-2, their combination with Fondy could not be regarded as meeting the unique features of the method of the present invention. Applicants respectfully request withdrawal of this rejection.

Claims 42-53 were rejected as obvious under §103 from Fondy in view of Kedar, Ten Hagen, Anderson and Ochoa. This rejection is also respectfully traversed.

Claim 72 replaces claim 42, and attention is respectfully invited to lines 3 and 4 of claim 72, as well as the last six lines thereof.

Fondy, Anderson and Ochoa have been discussed above, and applicants' commentary above is respectfully repeated by reference.

Kedar does not teach the use of MLV-encapsulated cytokines. To the contrary, Kedar refers to **unilamellar** liposomes for encapsulating the IL-2 as well as doxorubicin. The use of MLV-encapsulated cytokines enables the delivery of the cytokine to the retculoendothelial system (also referred to as mononuclear phagocytic system) and lymphoid tissue draining the area of injection, where it exerts its biological effect as an immunostimulator, but is clearly inefficient as to the systemic delivery of the cytokine to the tumor site. Against this, when encapsulating a cytokine, for example, in sterically stabled **unilamellar** liposomes (SSL), its predominant biological effect is exhibited at the tumor site.

In addition, Kedar does not teach the administration regimen of the present invention as detailed above. In fact, Kedar describes the effect on tumor cells of liposomal IL-2 (lip-IL-2) as compared to free IL-2 and the effect on tumor cells of doxorubicin encapsulated immunoliposomes (immlip-Dox) as compared to its effect when encapsulated in small liposomes (lip-Dox). There is no teaching or suggestion for a treatment

combining lip-IL-2 and lip-Dox, all the more to the specific treatment regimen of the present invention.

The rejection also asserts that in addition to the teaching of Fondy, Anderson, Ochoa and Kedar, Ten Hagen teaches the use for antitumor therapy of STEALTH liposome-encapsulated TNF-α (TNF-SL) in combination with STEALTH liposome-encapsulated Dox (Dox-SL). However, in addition to the differences between TNF-α and other cytokine as detailed in applicants' response to the previous Office Action (e.g. it not being a typical immunostimulator and being highly toxic), it should be pointed out that Ten Hagen makes use of TNF-α in combination with Dox in order to increase the permeability of the blood vessels at the tumor site. Ten Hagen does not describe the encapsulation of the cytokine in MLV as the authors would not preferably direct the drug to the tumor.

Further, while Ten Hagen describes the combination of TNF-SL with DOX-SL, there is no time interval between administration and no such time interval is suggested. In fact Ten Hagen relies on the simultaneous treatment with DOX-SL and TNF-SL because the synergistic effect is the result of TNF-SL inducing an increase of DOX-SL localization in the tumor.

Even if the references were obviously combinable, not accepted by applicants, such references in combination

would not lead the person of ordinary skill in the art to applicants' claimed invention. Applicants' invention as claimed is non-obvious, and applicants respectfully request withdrawal of the rejection.

Favorable reconsideration and allowance are earnestly solicited.

Respectfully submitted,

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